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Highlights

- First operational research study of hospital transfusion systems in a disaster
- A new approach to planning for these increasingly prevalent events
- Unique access to empirical data from the UK's largest post war mass casualty event
- Model outputs focusing on patient outcomes over system efficiency
- Translation of results into policy through key stakeholder consultation

Development of a discrete event simulation model for evaluating strategies of red blood cell provision following mass casualty events.

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Abstract:

Timely and adequate provision of blood following mass casualty events (MCEs) is critical to reducing mortality rates amongst casualties transported to hospital following an event. Developing planning strategies to ensure the blood transfusion demands of

casualties are met is challenging. Discrete event simulation (DES) offers a novel solution to this problem which is financially efficient, less disruptive to services and allows for rich experimentation compared to the current industry standards of live exercises, round-table discussion or tabletop planning. There are currently no published models of this type for investigating blood provision in MCEs. The objective of this study was to develop a working model which could be used to target the in-hospital 'levers' and 'supply levels' of the transfusion system and improve outcomes during the response to future events. This was achieved through the robust design of a DES model using exclusive access to qualitative and quantitative data as well as a panel of experts from the field of transfusion and MCE management. The completed model was extensively and formally evaluated with secondary data from the 7th of July 2005 London bombings, the largest UK based civilian MCE in over 50 years. A subsequent sensitivity analysis revealed the five factors displaying the greatest influence on casualty outcomes. Experimental themes based on these findings have generated new solutions for managing future events which have since been presented to MCE stakeholders and policy makers.

1. Introduction

Mass casualty events (MCEs) such as large scale transportation accidents or acts of terrorism require health organisations to adopt extraordinary measures in order to mount an adequate and sustainable response to the precipitating incident (Ryan and Doll 2012). In the UK, major trauma centres (MTCs) are at the epicenter of the hospital based response to these events, tasked with managing a sudden influx of severely injured casualties whose demand for resources carries a considerable risk of outweighing supplies (Arnold, Halpern et al. 2004, Einav, Aharonson-Daniel et al. 2006).

Amongst the population of casualties admitted to hospital following MCEs, approximately two thirds have been shown to die as a result of bleeding, half of these deaths occur within four hours and 95% within 24 hours of injury (Aylwin, König et al. 2006, Shapira, Adatto-Levi et al. 2006). Reducing in-hospital mortality in this patient cohort requires early surgical intervention to control bleeding in conjunction with the

rapid transfusion of blood, primarily through the use of packed red blood cells (RBCs), to restore circulating blood volume (Dutton 2012). The latter generates a massive strain on hospital blood banks and transfusion services to meet casualty blood demands within a finite period of time (Shinar, Yahalom et al. 2006).

At present the best approach for effectively managing this strain on MTC transfusion services is unclear. This is partly due to a lack of full understanding surrounding how the system operates under the surge conditions of an MCE, during which data collection and experimentation are of a low priority. Operational research techniques offer one approach of investigating in greater depth a relatively inaccessible and complex system such as this. Such techniques provide the opportunity to interact and experiment with the numerous highly variable component parts and people involved in the delivery of transfusion services during an MCE without impacting upon the delivery of patient care. Only having done this can we begin to identify the 'levers' within this system which offer the greatest potential for improving its performance and therefore the outcomes of bleeding casualties following such events.

The process of systems experimentation can take many forms. Physical models such as mock-up hospitals or table-top exercises have been used for many years in MCE contingency planning (Hsu, Jenckes et al. 2004, Koenig and Schultz 2009, Mackway-Jones 2012). Whilst this approach is effective in familiarising staff with procedures and identifying the logistical issues encountered in the unfamiliar circumstances of MCEs, experimentation in these scenarios is often limited. This is primarily due to the financial constraints, degree of service disruption and the level of complexity which can be incorporated into the model, given all inputs and outputs must remain manageable and interpretable at a human level of understanding (Hsu, Jenckes et al. 2004, Bartley, Stella et al. 2006, Norman, Stuart-Black et al. 2006, Gillett, Peckler et al. 2008).

In contrast to this physical modelling approach, mathematical models and computer simulation offer a more time and economically efficient approach to better understanding these types of complex problems, whilst preventing the disruption of key public services which may occur during live physical exercises. It must be appreciated

that these events are historically rare and by their very nature, often unpredictable, making empirical data sparsely available and providing little opportunity to experiment with, and improve system performance with methods such as Plan Do Study Act cycles or Lean (Young, Brailsford et al. 2004). Furthermore, issues of scarce resource allocation, resource competition dilemmas and queue minimisation inherent to transfusion service delivery during an MCE, are problems for which discrete event simulation (DES) was specifically designed and therefore suited for (Roberts, Russell et al. 2012).

The overall objective of this study was to develop the first of its kind, working DES model of an MTC transfusion system under the surge conditions of a generic MCE. The model is based on data from the largest recent UK based MCE for several years – The London Bombings of July 7th 2005, with the intention of extrapolating from this experience to consider the management of other MCE's and notably scenarios where the system has to cope with higher RBC demand, beyond the surge capacity. This was achieved through three sequential processes. Firstly, the model was exactly developed using the unique opportunities afforded by the study institution, which provided access to robust quantitative clinical data, as well as, primary qualitative input from a panel of experts in the field. Secondly, the developed model was extensively and formally evaluated, again utilising exclusive data from hospital records relating to the London 7/7 bombings. Finally, a sensitivity analysis was performed to provide an indication of which system factors exerted greatest influence on outcomes and therefore could be presented to MCE policy makers and stakeholders as a potential means of reducing critical mortality in future events.

2. Related Work

This article is the first to describe the development of a model purposed with evaluating different RBC management strategies in the context of an MCE, although related experimental findings have already been published by this research group (Glasgow, Vasilakis et al. 2016). Collectively with this previously published work, this model represents the first transfusion specific DES study in the context of an MCE.

The concept of applying operational research to problems in healthcare is not new and has continued to grow in popularity, especially within public sector services (Simpson and Hancock 2009, Thorwarth and Arisha 2009). In particular, there have been a number of recent examples focusing specifically on the use of DES to solve healthcare problems. For example, Baril et al applied DES to reduce delays in the time to treat haematology patients attending outpatient appointments (Baril, Gascon et al. 2016); Willoughby et al have seen their use of simulation to develop strategies for improving patient flow within speech and language services successfully adopted into clinical practice (Willoughby, Chan et al. 2016); Abo-Hamad and colleagues published results of a simulation model which illustrated the importance of facilitating the outflow of patients from an emergency department as opposed to merely increasing departmental resources, as a method of managing demand on healthcare services (Abo-Hamad and Arisha 2013); Ahmed et al also simulated emergency department throughput, improving service delivery in their model through the better allocation of available staffing across the department (Ahmed and Alkhamis 2009); and finally, Mielczarek utilised simulation in her study to forecast emergency service workloads and demonstrate the tool's potential for informing healthcare policy on a wider, more regional scale (Mielczarek 2014).

Although the range of operational research techniques applied to healthcare problems has remained relatively broad, the majority of MCE specific models to date have focused primarily on the pre-hospital care aspect of MCE preparedness. Examples include: scene casualty clearance using mixed integer programming models (Dean and Nair 2014); development of a general decision support rule to aid casualty triage (Mills 2016); emergency vehicle routing using constraint programming and column generation models (Amadini, Sefrioui et al. 2013, Sung and Lee 2016); pre-hospital care team performance and casualty processing studies using optimisation modelling (Wilson, Hawe et al. 2016); scene casualty decontamination modelling (Egan and Amlôt 2012); and pre-hospital resource capacity assessment using simulation models (Wang, Luangkesorn et al. 2012).

Comparatively, the investigation of in-hospital based care during the response to MCEs using operational research is less abundant. This may be due to the comparatively inaccessible nature of in-hospital systems and the data sets required studying and analysing these events, a key aspect to this study's success. Furthermore, there has previously been a popularly held misconception that resources including blood are always adequate for a hospitals' capacity to deliver them following an MCE. This theory has been challenged in a number of published studies, which when coupled with the growing frequency of these events and an ever evolving global terror threat, highlights the need for this type of research more than ever (Schmidt 2002, Hess and Thomas 2003, Gutierrez De Ceballos, Fuentes et al. 2005, Cohen 2006, Shinar, Yahalom et al. 2006, WHO 2007, Soffer, Klausner et al. 2008, Deely, McClean et al. 2010, GTD 2011, Office 2011, UK 2011, Rode 2013). One of the few and earliest examples of in-hospital MCE modelling is a study of surgical resource utilisation following urban terrorist bombings by Hirshberg et al in 1999 (Hirshberg, Stein et al. 1999). This study used computer simulation to analyse and optimise the surgical care based elements required when responding to these events. The study identified mathematical modelling and simulation as a beneficial and powerful adjunct to hospital based planning for MCEs. Specifically, this work identified the assessment of a hospital's capacity to accept casualties from an event at that time, as being overly optimistic (Hirshberg, Stein et al. 1999).

Several years later, this research group revisited in-hospital simulation in MCEs with a study investigating the relationship between casualty load and the level of overall trauma care which could be provided to the victims. They identified the surge capacity of a responding unit and offered a quantitative definition of a hospital's capacity to cope following an MCE (Hirshberg, Scott et al. 2005). The study also showed the rate of casualty arrival as a principal determining factor in the ability to adequately treat casualties, a finding echoed in another simulation study of MCEs by a group from Kansas State University in the USA (Hirshberg, Scott et al. 2005, Joshi 2008).

The specific investigation of consumable resources in MCEs using mathematical modelling has surprisingly only been studied on only a few occasions. Abir et al at the

University of Michigan in the USA designed a simulation based model to predict surge capacity bottlenecks for burn mass casualties at hospital. They found medical units in this case would be limited early in the course of such an event through their bed capacity, followed by consumable treatments such as Sulfadiazine, albumin and importantly, blood type AB RBCs. This is the only computer simulation study in the context of MCEs which discusses resource consumption in terms of blood products and does so, solely in the context of mass burns (Abir, Davis et al. 2013).

Non-MCE based blood modelling is far more common with a number of studies having utilised simulation to investigate all stages of the blood provision supply chain (Beliën and Forcé 2012). Katsaliaki et al and Kopach et al both investigated policies for improving blood inventory management within hospitals through a simulation based approach (Kopach, Balcioglu et al. 2008, Katsaliaki and Brailsford 2016); Baesler et al took a more central approach in their simulation study of practice within central blood centres, generating more flexible inventory management strategies (Baesler, Nemeth et al. 2014); and finally, Mustafee et al and Gregor et al both developed simulation models for finding distribution based solutions to balance blood centre supply with hospital based demand (Gregor, Forthofer et al. 1982, Mustafee, Taylor et al. 2009).

Interestingly, the MCE focused study by Abir et al identified factors such as ventilator availability and other critical resources, normally expected to provoke concern earlier than blood products in the MCE response, to be adequately available for the needs modelled (Abir, Davis et al. 2013). Other historical models of resource consumption and MCE requirements include functioning generic prediction tools by the Chicago Department of Public Health and a surge model by the Agency for Healthcare Research and Quality (AHRQ) (Roberts, US Department of Health and Human Services). These provide an estimated needs assessment of resources based on the size and type of event by means of interactive stand alone or web-based program respectively. Whilst providing an overall approximation of resource needs they do not consider the state of supplies available already at the responding centres, neither do they map the consumption of these supplies as casualties are treated over time. The ability to model variability and make the generalised assumptions necessary for planning such events is

what allows a mathematical modelling approach to be applied across a wide range of scenarios and problems, providing quantitative results which, as expected in this study, can be interpreted and translated into real life practice.

3. Model Development

3.1. Model Limits

We limited the model to a single generic UK based major trauma centre (MTC) and included only the transfusion related processes involved in managing casualties within the confines of the hospital following a non-specific single incident MCE. Casualties at risk of traumatic haemorrhage following MCEs are of two triage types – priority one (P1) and priority two (P2), both of which are managed at MTCs. P1 casualties are the most critically injured and by accepted definition require immediate (<1 hour) medical intervention (Mackway-Jones 2012). This group are therefore more likely to require a transfusion and in greater volumes compared to P2s, who whilst still requiring urgent (<4 hours) treatment are less severely injured than P1s (Mackway-Jones 2012).

Due to recent changes in the use of blood components other than RBCs in the management of traumatic haemorrhage such as clotting factors, we decided to concentrate primarily on RBC delivery in the first model of this kind (Borgman, Spinella et al. 2011, Davenport, Curry et al. 2011). The timeframe of the simulation covered the first 72 hours from the time of arrival of the first P1 or P2 casualty at the MTC following an event. This period therefore encompassed the immediate surge in casualty arrivals during which the demand for blood is greatest, through to the beginning of the recovery phase of an event when restocking of supplies is more feasible (Ryan and Gavalas 1998, Bowley, Rein et al. 2004, LESLP 2012).

3.2. The Processes of RBC Provision at an MTC Following an MCE

Casualties arrive at an MTC emergency department (ED) following an MCE triaged as either P1 or P2, other triage categories being managed at alternative sites. Their arrival rate follows a classical pattern of initial surge followed by a gradual decay, with the peak in arrivals reached around one hour following admission of the first severely injured

casualty (Raiter, Farfel et al. 2008, Shultz 2008, Prevention 2011). Upon arrival, casualties are assessed by a trauma team and their bleeding status is determined. During this time, intravenous access is gained on all P1 and P2s, this facilitates the transfusion of blood if required and allows collection of a blood sample for laboratory processing. All arriving casualties are assigned a unique hospital number on admission which serves as a specific identifier for blood samples and the treatment they receive within the MTC. Casualty RBC demands are met through the processes described in the Unified Modelling Language (UML) activity diagram in Figure 1, which also serves as a model map.

Once bleeding casualties are identified treatment can commence immediately through the use of emergency universal donor type O RBCs which are stored within the ED and other critical areas. These RBC units are compatible with all patient blood types. Simultaneously, the casualties' blood sample is sent to the transfusion laboratory for individual blood group analysis. This allows transfer of the patient onto treatment with their own specific blood group matched RBCs as soon as the sample processing is complete and blood type verified. The aim of this is to preserve the finite supplies of universal donor type O RBCs within the hospital for treatment of newly arriving casualties.

Blood samples are automatically transported to the transfusion laboratory via a pneumatic air tube system. On receipt of a new blood sample in the laboratory, the transfusion technician verifies the sample and books it onto the MTC computer system. The sample is then spun on a centrifuge prior to analysis. Centrifuges do not generally allow continuous loading, although multiple samples may be spun during any single run. Following this, samples are checked prior to being manually loaded onto an automatic blood group analyser which can accept the continuous loading of samples. Once the blood group has been automatically determined, the sample is manually registered as grouped on the system and the corresponding casualty can then receive type specific or any compatible RBCs available.

Transfusion of casualties continues as long as compatible RBCs are available (including emergency type O RBCs) in the form of packs of blood containing up to six units of RBCs at a time until such time as the casualties' blood demand is met. During this time the casualty is also receiving all additional therapies required to treat their injuries, such as surgical interventions in the operating theatre to control bleeding or medical treatment on the critical care unit to restore their physiological state. RBCs other than emergency type O are not always available in these critical areas and therefore require manual portering from the transfusion laboratory to the patient within the MTC. The overriding aim is to ensure the rapid delivery of RBCs in order to meet a casualty's blood demand with as much of this blood volume in the form of patient specific type matched blood as possible.

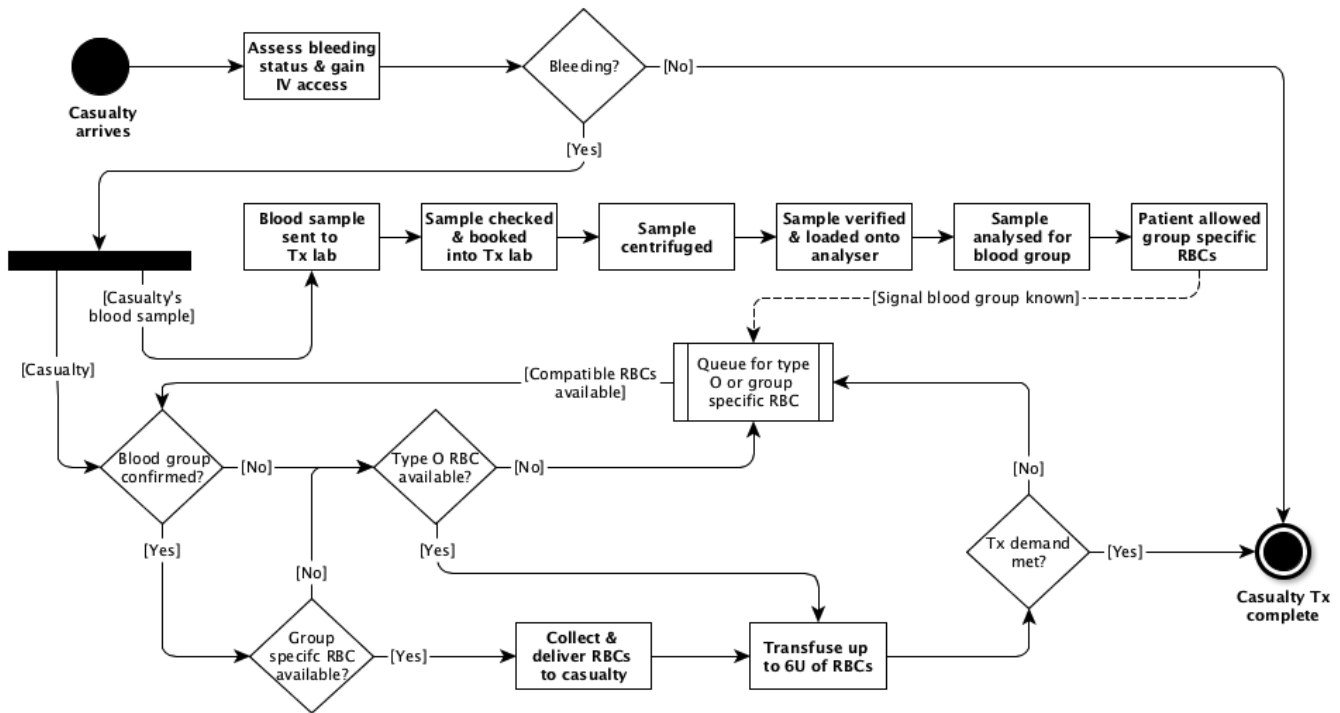


Figure 1: Unified Modelling Language (UML) activity diagram of the process of providing P1 and P2 casualties with RBCs within an MTC following an MCE. The process initiates with arrival of a casualty and completes once their transfusion requirements have been met. The processes involved in meeting transfusion requirements follow the directional flow indicated by the arrows between various actions, these include: Activities: Decisions: Queues: Divisions (into 2 linked & identical entities): . Tx = Transfusion.

3.3. Model Implementation

The model was implemented in Arena Simulation Enterprise Suite version 14.0 (Rockwell Automation, Pittsburgh, USA) following inspection of alternative available software packages using the weighted average system for software evaluation (Collier, Carey et al. 1999, Jadhav and Sonar 2009). The model was developed through both direct observations of the processes involved in RBC provision, as well as in depth discussion with a panel of MCE transfusion experts from various disciplines. Further details regarding the model construction, including examples of the entities and modules

included are available via the supplementary online material. The final evaluation model included a number of simplifying assumptions agreed amongst the expert panel in order to manage the inherent system complexity without compromising on the applicability of the model, these included:

- Only P1 and P2s casualties were included in the model with other triage categories assumed to be treated elsewhere at less specialised units to prevent them impacting on the management of the most severely injured casualties.
- The triage state and the initial RBC requirements of arriving casualties was assumed to remain unaltered once admitted to the MTC irrespective of time within the model.
- P1 casualties were prioritised over P2s in all processing or treatment queues throughout the model to reflect their critical state and the narrow window of time in which they require treatment. Further queue priority decisions were based purely on a first in first out system.
- The MTC was assumed to be in a zero state on arrival of the first casualty to reflect the time classically afforded to hospitals to prepare between the declaration of an MCE and the arrival of severely injured casualties.
- No human errors or system failure episodes were included in the simulation.
- All treatment resources aside from RBCs, transfusion staff and processing equipment were deemed adequate for this transfusion specific model.
- Type O universal donor (emergency) RBCs, when in stock, were assumed to be immediately available in all urgent areas via standard satellite fridges within the MTC.
- RBCs were provided to casualties in order of casualty compatibility and abundance of availability, with emergency type O RBCs provided only if no other alternative was available. For example, a casualty of blood type AB (a universal recipient who can receive transfusion of any blood type) will receive type AB blood above all others, as this cannot be transfused to non-AB type casualties. Whereas, If no type AB blood is available, the model allocates the type of blood that is most abundant at the time e.g. type A or B. Type O is the last to be allocated due to it's value as the

universal donor type, which may be given to any casualty and hence its initial use in emergency transfusions.

3.4. Data Inputs

The inputs required to drive the model included casualty parameters, blood processing times, treatment times and resource levels such as RBC units and transfusion staff levels as summarised in Table 1. The inputs were informed using a variety of sources, these included; a comprehensive literature review covering 100 years of MCEs (Glasgow, Davenport et al. 2013), a questionnaire of all four MTC transfusion services based in London, UK (all four responded in full) and interrogation of both civilian and military trauma patient databases. The literature review provided data concerning casualties received, their arrival rate and the blood type distribution amongst casualties. The questionnaire was followed up with repeated dialogue with transfusion laboratory managers and site visits to determine processing time variation and mean capacity for sample processing across MTCs as well as transfusion staff numbers. The civilian and military databases were sourced as surrogate datasets for data not available for direct collection, this included casualty bleeding rates and blood demands amongst P1 and P2s, their processing times and the to time transfuse individual RBC units.

The assimilated data was analysed using Arena's inbuilt input analyser tool and where required, the curve fitting software package - EasyFit Professional version 5.5 (MathWave Technologies, 2004-2010). This provided the probability distributions applied to each input parameter within the model. Those inputs requiring absolute measures such as RBC stock held, were taken as the mean value across all MTCs examined (Table 1).

Table 1 A summary of the data sources and input values for each simulation parameter

Input Parameter	Data Source	Input Description
Casualty Arrival Rate	Literature Review	Johnson SB Distribution ($\gamma = 1$, $\delta = 0.55$, $\lambda = 15$, $\Upsilon = 0.05$)
Casualty Load	Literature Review	Constant 40 Casualties
Casualty Blood Type	Literature Review	A = 42%, B = 10%, AB = 4%, O = 44%

Proportion of P1:P2s	Literature Review	P1 = 60%, P2 = 40%
Assessment and Access Time	Civilian Surrogate Data	Gamma Distribution P1 = ($\alpha = 2.1$, $\beta = 5.0$), P2 = ($\alpha = 1.7$, $\beta = 11.0$)
Proportion of P1 & P2s Bleeding	Military Surrogate Data	P1 = 80%, P2 = 50%
P1 & P2 RBC Demand	Military Surrogate Data	Poisson Distribution: P1 = (10.7), P2 = (4.7)
Blood Sample Transport	MTC Survey	Constant 3 Min
Book & Verify Sample	MTC Survey	Constant 1 Min
Centrifuge Sample	MTC Survey	Constant 5 Min
Verify Sample & Load Analyser	MTC Survey	Constant 1 Min
Analyse Sample	MTC Survey	Constant 11 Min
Unload Sample & Verify	MTC Survey	Constant 1 Min
Full Antibody Screen on Analyser	MTC Survey	Default Group Only, Full Screen Uses TRAI(25,35,90)
Dispense Grouped RBC	MTC Survey	Constant 30 Seconds per Unit of RBC
Delivery of RBC	MTC Survey	Constant 5 Min
Transfusion Time	Civilian Surrogate Data	Johnson SB Distribution: P1 = ($\gamma = 2.1$, $\delta = 0.75$, $\lambda = 29.0$, $Y = 0.56$), P2 = ($\gamma = 1.2$, $\delta = 0.62$, $\lambda = 29.0$, $Y = 0.84$)
Technicians	MTC Survey	6
Porters	MTC Survey	4
Centrifuge Capacity	MTC Survey	15 samples*
Analyser Capacity	MTC Survey	180 samples
Type O RBC Units Held	MTC Survey	100
Type A RBC Units Held	MTC Survey	75
Type B RBC Units Held	MTC Survey	25
Type AB RBC Units Held	MTC Survey	10

* MTCs reported an average of 2 available centrifuges each with an average sample capacity of 15 samples.

Note: All distribution parameters were obtained by the curve fitting software tool EasyFit.

3.5. Simulation Experimentation

We designed the model to be used for investigating RBC provision across a range of MCE sizes and applied conditions. The effects of system modifications on model performance were planned to be measured through the use of two principal outcomes:

1. The time point at which emergency type O RBC inventory levels were exhausted (a surrogate measure of the hospital's inability to continue receiving patients given that no immediate life-saving treatment can be provided to bleeding casualties when type O RBC stock runs out).
2. The percentage of bleeding P1 and P2 casualties receiving their required level of transfusion within the time allocated by their triage category (within one hour for P1s and four hours for P2s according to established clinical guidelines) (Mackway-Jones 2012).

In order to evaluate the model the simulation was setup following its construction as summarised in Table 2. Run statistics were set in Arena to be collected at the end of each run in addition to continuous parallel in-run recording of data into Microsoft Excel (Microsoft Corp. Redmond, WA, USA). The number of replications performed per experimental condition was calculated using a confidence interval analysis of the mean output of each of the principal study outcomes considered in terms of the overall cumulative mean across runs. A confidence interval of 5% was applied based on best practice and 100 replications was identified as providing a sufficient balance between experimentation time and performance accuracy within the model (Robinson 2004, Karnon, Stahl et al. 2012).

Table 2 Summary of simulation run-setup parameters applied to the model

Parameter	Setting
Replications	100

Statistics Collection	End of run as well as continuous data collection via VBA
Date and Time Stamp	Present Day
Warm-up Period	0 Minutes
Replication Length	72 Hours
Hours per Day	24
Base Time Units	Minutes
Inputs	Parameter dependent: Defined constant value or random sampling of specified probability distribution
Output	Transient
Queue Management	First in first out as resource availability dictates
Run type	Batched runs
Real-time or End-point Analysis	End-point Analysis

The length of the simulation as discussed was restricted to the first 72 hours following an event to encompass the time of maximum RBC demand. This time represented the only terminating event with casualties permitted to arrive for the duration of this time, although the likelihood of a casualty arriving after 12 hours was extremely rare from the probability distribution sampled for casualty arrivals. This is in keeping with the chances of a viable P1 or P2 casualty being evacuated in a salvageable state from the scene of an MCE so long after an event. The base time units used in the model were minutes in keeping with the defined data inputs used to inform the model.

4. Model Evaluation

4.1. The Evaluation Process

We evaluated the simulation model to determine whether its baseline state is an adequate representation of the system it was designed to imitate. We conducted the evaluation through three interconnected processes: Verification, testing and validation (Balci 1994).

4.2. Model Verification and Testing

Verification of the model was performed using both visual confirmation of the model through Arena's interactive animation environment, as well as inspection of the source code of the simulation. This process included running constant value inputs through the model in order to check expected outcomes were delivered by the simulation. Furthermore, this approach permitted complete testing of the model and elimination of source code errors. For example, if following a completed run of the model the RBC stock level of group A blood was found to be a negative value, this would imply the incorrect delivery of RBCs to casualties, when in fact supplies were exhausted. The complete verification and testing process required 53 model revisions from version 1.0 through to version 5.3 and involved approximately 80,000 simulation runs before a final satisfactory baseline model was reached.

4.3. Model Validation

4.3.1. Design Validation

Validation of the model design and the input values used to drive it were determined during the conceptualisation phase of the study and throughout its development. The panel of experts who performed this phase of model evaluation was formed of 12 specialists including: Biomedical scientists, blood bank managers, pre-hospital care physicians, trauma surgeons, haematologists and emergency department physicians and nurses. Panel members had either had first-hand experience of such an event themselves or were actively involved in planning future MCE transfusion strategies. Similarly, the white-box validation, whereby the components in the computerised model and their interactions were assessed for accuracy was a continuous process during the model's development. Again, the expert panel ensured continuity between the validated paper-based model and the working Arena model construct.

4.3.2. Black box validation

Through black-box validation, often regarded as the most important aspect of the validation process, we assessed the input and output relationships of the model (Robinson 2004). In particular, we compared the real-world system with the model using identical inputs and observing the outputs produced. At the time of this work, the London bombings of July 7th 2005 was the most recent large-scale MCE experienced in the UK for which casualty documentation and blood use were recorded and potentially accessible to the investigators. This event was therefore selected to validate the model with, using data from casualties received at a single centre – The Royal London Hospital (RLH) following the event. The RLH was selected as the study centre as this MTC received the majority of P1 and P2 casualties on the day of the bombings.

All P1 and P2 casualties treated at the RLH on the day of the bombings were included in the comparison study. Information relating to these casualties was obtained through a number of separate avenues, these included: Analysis of the RLH transfusion laboratory data registry, examination of individual computerised health records relating to the event and discussion with both RLH biomedical scientists and transfusion laboratory managers, who were either involved or had in-depth knowledge regarding the event and the response at the RLH. These sources were examined for all available data relating to casualty arrival and processing times, the individual use of group-specific and emergency type O RBCs and the transfusion related timings of all units requested. The assimilated data was then collated for analysis.

The model was designed to provide RBC units to casualties on a continuous basis until such time as their initial RBC demand was met and they were therefore deemed as treated to survival in terms of haemorrhage. In order to account for this when interpreting and comparing the real data from the event with the model output, the time to meet each individual casualty's RBC demand from the real data was calculated as follows:

$$\sum_{j=1}^{T_i} (C_{ij} - R_{ij}), \quad i = 1, \dots, n$$

Where

- T_i is the total number of RBC transfusions required by patient $i = 1, \dots, n$
- R_{ij} is the time the j th transfusion for the i th patient is requested
- C_{ij} is the time the j th transfusion for the i th patient is completed.

In order to maintain the anonymity of casualties treated at the RLH, the bleeding casualties who were directly compared with the model outputs were assigned an alphabetic identifier based on their RBC demand as opposed to their order of arrival.

Following collation of all available data, the Arena based simulation model was set to replicate the initial state and response of the RLH on the 7th of July 2005; this included programming the model with the following inputs:

1. The resources including number of transfusion staff available and shelf-stock levels of each group of RBCs were set to the actual RLH values of the day.
2. The individual P1 and P2 casualties were programmed to arrive at the exact time that they did on the day of the bombings.
3. The P1 and P2 casualties who did not require a transfusion in the initial 72 hours of the event were also assigned not to require a transfusion in the model.
4. Those P1 and P2 casualties who did require a transfusion in the initial 72 hours were set to require the same exact volume they received during this timescale in the model as they did in real-life.
5. All P1 and P2 casualties entering the model were assigned their real blood type during the simulation to replicate the demand on type specific RBC stock levels.
6. The restocking of emergency type O RBCs was included in the model to replicate the volume and time of arrival of these requests at the RLH on the day of the bombings. This additional model component exerted no further effect on any other aspect of the model aside from increasing the level of type O RBC held at the designated time of activation, precisely mimicking the real-life events.

All other data inputs and model parameters as previously described (Tables 1 & 2) remained unchanged. All data from both the real event and the model outputs were collated in Microsoft Excel and all subsequent data analysis was performed in GraphPad Prism (GraphPad Software Inc. San Diego, CA, USA).

The alternative hypothesis for the validation study was that there is a significant difference between the outputs of the simulation model and the 7/7 comparison study data when the inputs of the 7/7 event are applied. Conversely, the null hypothesis was that there is no significant difference between the model and real scenario outputs. Although not proving the null hypothesis to be true, rejecting the alternative hypothesis was seen to provide greater confidence in the model as being valid for the intended purpose. The alternative hypothesis was tested by calculating the confidence interval (CI) for the difference in means between the simulation model and the actual event data using the Student's t-distribution and a significance level (α) set at 5% (Law and Kelton 2000).

The examination of casualty hospital and transfusion records as well as the material yielded through dialogue with the RLH transfusion personnel provided the following information. On the day of the attacks the RLH received 27 P1 and P2 casualties over approximately three and a half hours, with the first arriving at 10:05am and the last at 1:20pm. From the 27 casualties 19 were triaged as P2s, none of which received a transfusion during the initial 72 hours following the event. In contrast, from the eight P1s treated, seven (87.5%) required a RBC transfusion over this time. The individual RBC demand and processing times for the P1 casualties is shown in Table 3 accompanied by the changes in stock levels which occurred over the first 72 hours.

In total, 164 units (U) of RBC were used during the first 72 hours of the event, with over 70% being type O units. The median RBC demand by the seven transfused casualties was 18U (inter-quartile range (IQR) 11.5-34U) which was met in a median time of 61.0 minutes (IQR 49.0-114.0 minutes). The 100 replications of the model simulating the first 72 hours of the event produced a total RBC use in all replications of 164U. This was expected, as the individual RBC demand for the bleeding P1 casualties was set to

exactly replicate that of the real casualties and serves principally to demonstrate the model acts correctly. The group-mix of emergency RBC to type specific RBC provided to individual casualties was however not pre-set within the simulation setup. The 72 hour median, IQR and range of each group of RBCs across 100 replications of the simulation model is shown in Table 4 along with the actual values from the real event.

Table 3: P1 casualty timings, RBC use and effect on RBC inventory levels at the RLH following the London bombings of 7th July 2005

Casualty	A	B	C	D	E	F	G	H
Priority	P1	P1	P1	P1	P1	P1	P1	P1
Transfused <72 Hrs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
RBC Demand (Units)	49	40	28	18	14	9	6	0
Time to Meet Demand (Minutes)	167	126	102	61	59	39	30	N/A
RBC Grouping	O	A	B	AB				
Initial RBC Stock Level (Units)	168	102	18	18				
RBC Stock Consumption (Units)	121	26	17	0				
72 Hour RBC Stock Level (Units)*	277*	76	1	18				

*A total of three type O RBC deliveries were received on the 7th of July 2005 totaling 230 Units.

One of the principal outcome measures for the study was time to exhaustion of RBC stocks and specifically, emergency type O stocks. Although the RBC stocks did not reach exhaustion point during the event, it was possible to compare their final level at 72 hours with that produced by the model. The real 72 hour RBC level values all fell within the IQR of the results produced by the model and upon paired t-test analysis there was found to be no significant difference between the real event 72 hour RBC levels and the model output values (p-value = 0.80). This supports the rejection of the

alternative hypothesis that there is a significant difference between the model's outputs and those of the actual real-life event in terms of total units of each of the four blood groups consumed.

Table 4: The median, IQR and range of RBC levels at the 72 hour termination point for each blood group across 100 replications of the simulation model compared with the final values from the real event including the RBC restocks which occurred

RBC Group	Minimum	1st Quartile	Median	3rd Quartile	Maximum	72 Hour RBC Stock Level (real values)
O	243.0	265.0	272.0	277.3	289.0	277.0
A	65.0	74.0	80.0	89.0	102.0	76.0
B	0.0	0.0	0.0	2.0	18.0	1.0
AB	18.0	18.0	18.0	18.0	18.0	18.0

The other principal outcome measures required in realising the model objectives were the number of transfusion requiring P1 and P2 casualties treated within their defined time window of one and four hours respectively. As none of the P2 casualties received at the RLH required a transfusion within the first 72 hours, only the P1 cohort could be investigated. A comparison between the median and IQRs of the model outputs and the real event data is shown in Figure 2, this displays the number of transfusion requiring P1 casualties treated within increasing periods of time from their hospital arrival.

Nearly half of all the transfused P1s on the day of the bombings received their transfusion requirement within one hour based on their time from arrival to initiation of transfusion, combined with the interval from subsequent RBC requests to them being transfused. Similarly, the model showed a median of three P1s (IQR 2-4) treated within one hour of arrival and no significant difference between the real values and the model output across all time levels on paired t-test analysis (p-value = 0.35). Again, this would support the notion that whilst this does not prove the null hypothesis, we can reject the alternative hypothesis of a significant difference between the model's performance and that of real-life for this parameter.

4.3.3. Additional model validation

Due to the inability to evaluate the treatment of bleeding P2 casualties, a further validity assessment of the model was undertaken investigating the overall time for each individual casualty's RBC demand to be met, as well as the overall mean time across all casualties. The median (IQR) time to meet this demand in the model for the seven bleeding P1s was 67.5 minutes (32.4-130.4 minutes) across all replications. In the actual event, the median RBC demand by the seven transfused casualties was 18 units (11.5-34U) which was met in a median time of 61.0 minutes (49.0-114.0 minutes). The individual timings for these seven casualties are shown in Figure 3 along with their corresponding values from the real event. A paired t-test of the median model outputs and real event data showed no significant difference between the real event data and the model (p-value = 0.28). The 95% confidence interval for the difference in mean time to be treated between the model and the real event across all bleeding casualties spanned zero (-0.1625 to 2.305) and there was therefore no significant difference between the model and real-life distributions. Once again, the alternative hypothesis of there being a significant difference between the model and real-life was rejected and greater confidence could therefore be gained in the model's representation of real life events.

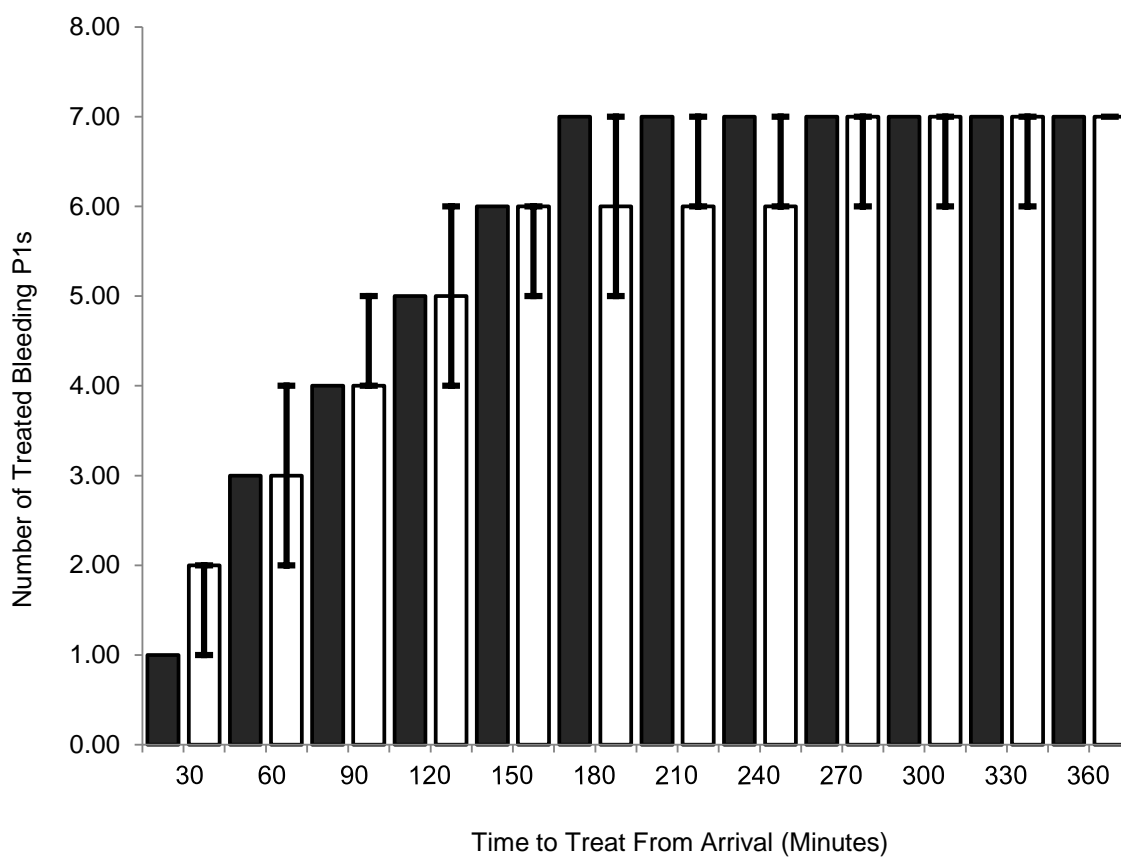


Figure 2: A comparison between the median and IQRs (whiskers) of the model outputs (□) and the real event data (■) showing the number of transfusion requiring Priority 1 (P1) casualties treated within increasing periods of time from their hospital arrival.

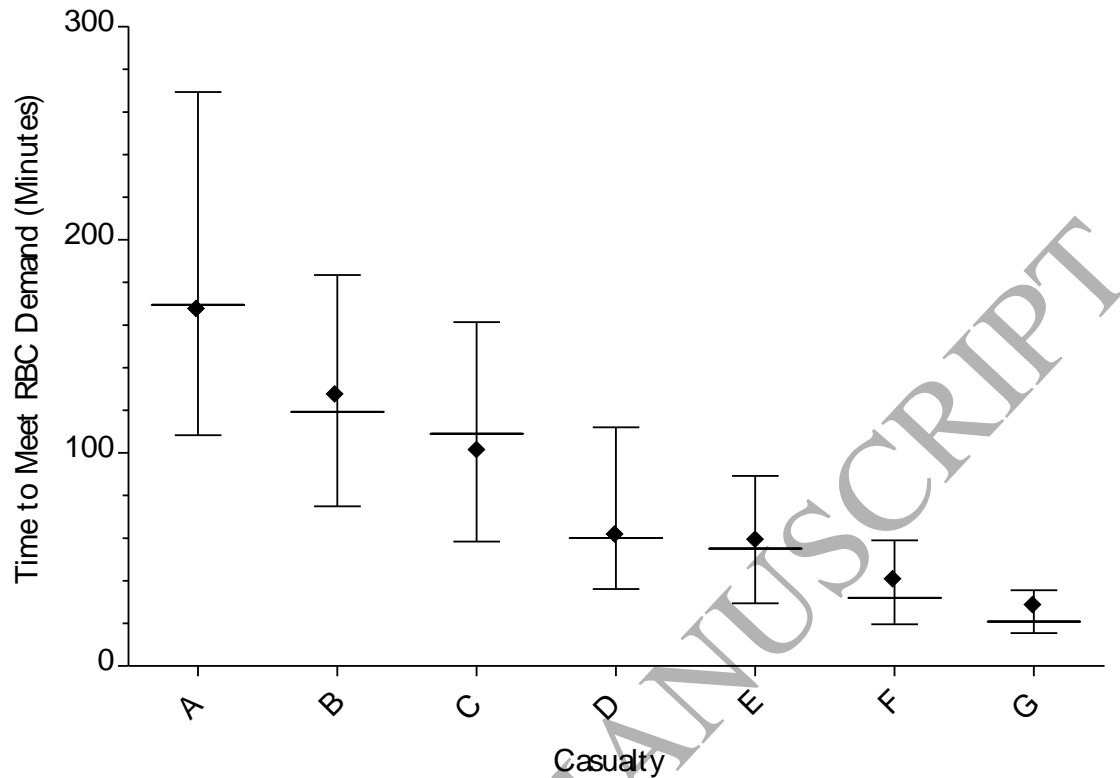


Figure 3: The median and IQR of times to meet the RBC demand of the individual bleeding P1 casualties following 100 replications of the simulation model, accompanied by the actual real life times (◆) for each corresponding casualty's RBC demand in 2005.

5. Sensitivity Analysis and Scenario Experimentation

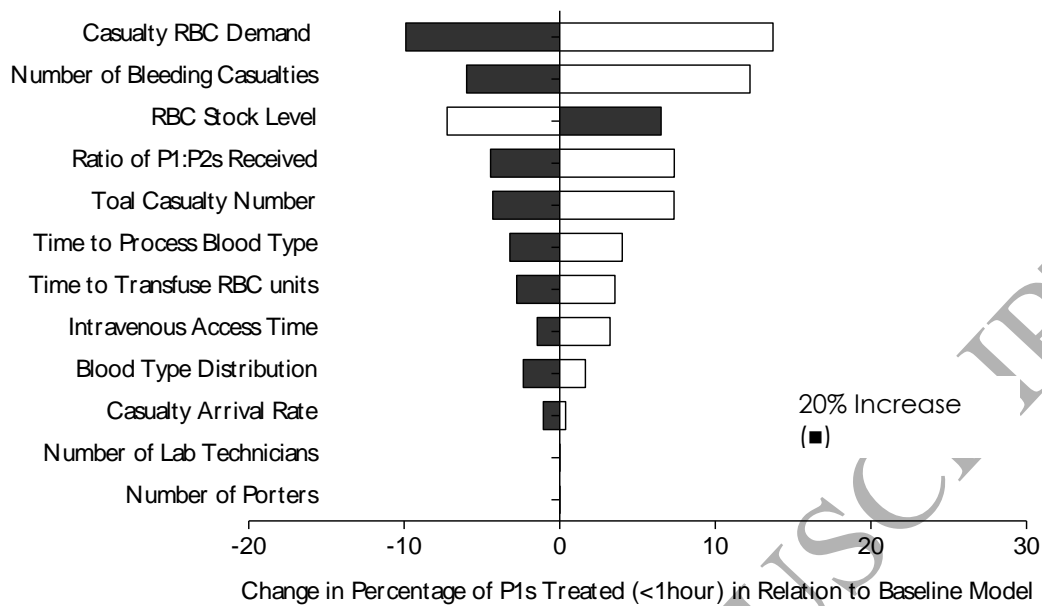
5.1 Sensitivity analysis

Sensitivity analysis is a type of experimental analysis applied to a model to establish the effect size each individual input parameter used to drive the model has on outputs during a set of simulation runs. The process serves three key purposes; it allows greater understanding of the importance of the model inputs derived from uncertain or surrogate data sources, it also indicates how robust the model is and therefore, how resistant the model is to changes to its inputs, finally it provides an initial yield of experimental information, as it demonstrates the effect changes in the model's

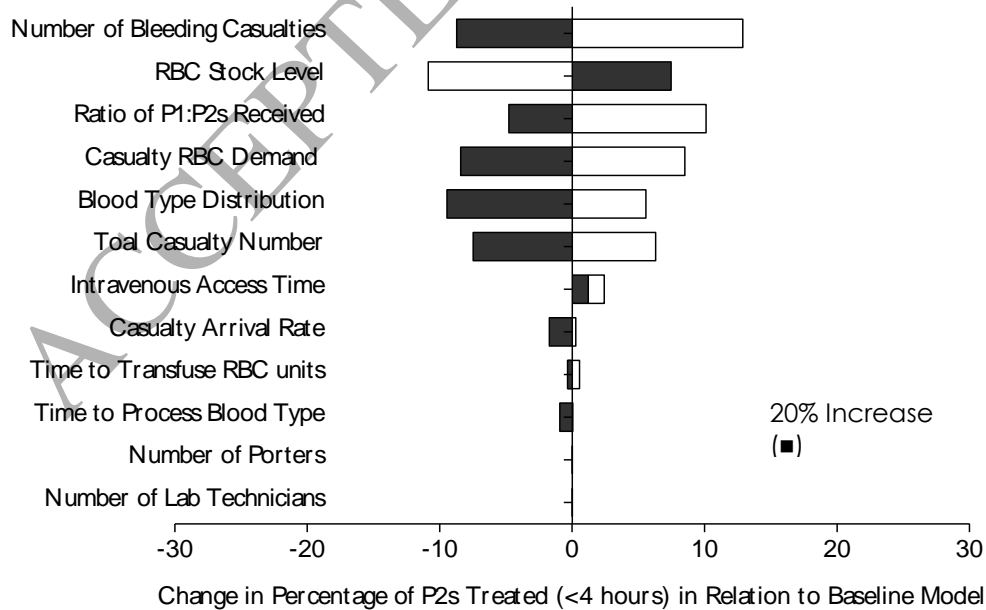
experimental components have on outcomes. This process therefore gives an early indication of the level of change required for a simulation run to produce an appreciable change in output (Robinson 2004).

Sensitivity analysis can be performed using various methods depending on the complexity of the model and study objectives (Robinson 2004). This study employed a one-way sensitivity analysis. This involved increasing or decreasing individual input parameters by a constant 20% of their baseline value and recording changes in outputs. This percentage change was chosen based on the literature discussion of performing a sensitivity analysis within a study of healthcare economics, a review of sensitivity analysis techniques and following a consultation with project stakeholders (Hamby 1995, Taylor 2009). During each batch of 100 runs of the simulation only a single parameter was changed at a time in order to identify individual factor effects. When the increase or decrease was in relation to a sampling distribution, the scale parameter of the distribution was scaled up or down by 20% of its baseline value. The sensitivity of the mean output results relating to bleeding P1 and P2 treatment percentages are shown in the tornado diagram of response effect in Figure 4.

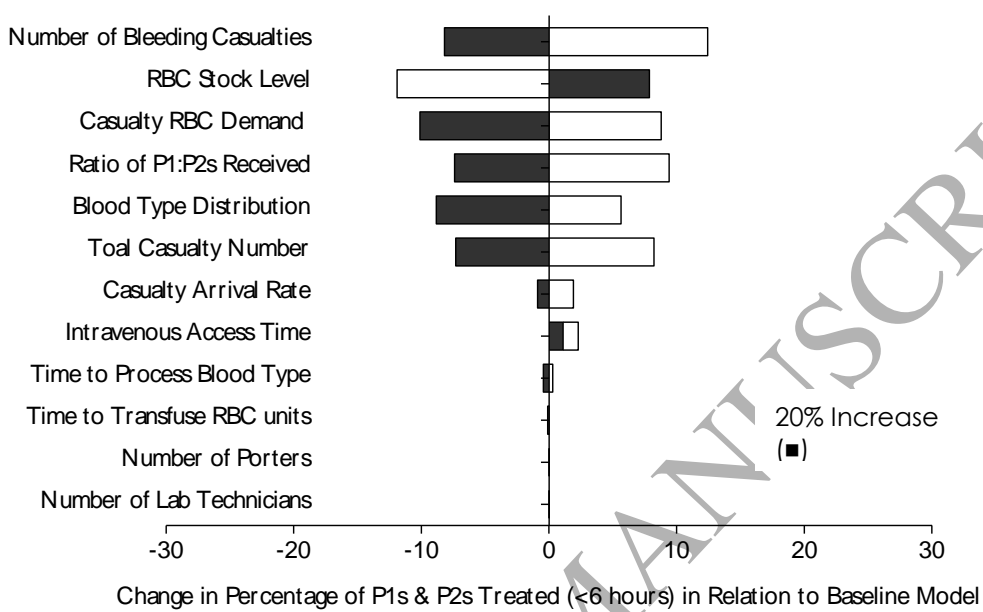
A)



B)



C)



D)

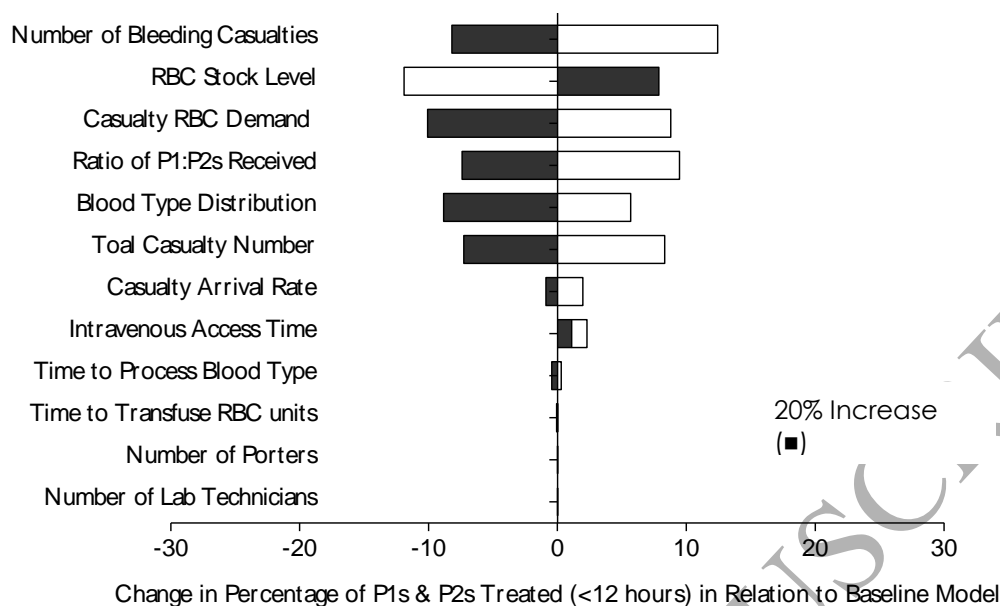


Figure 4: Mean percentage change of: A) percentage of P1s treated in full within 1 hour, B) percentage of P2s treated in full within 4 hours, C) percentage of P1s and P2s treated in full within 6 hours, D) percentage of P1s & P2s treated in full within 12 hours, following a 20% increase (■) or decrease (□) in input parameter values. CI widths were extremely small and are therefore not presented.

The magnitude of the response following a 20% increase or decrease in an input parameter's value can be described as having a large effect on the outcome measure when the change is approximately 10% or greater, a medium effect when the change is between 5-10% and a small effect when less than 5%. In terms of the percentage of P1s treated within one hour of arrival, a large effect is observed with a change in the percentage of bleeding casualties and the individual RBC demand of all bleeding casualties. The latter exhibits the greatest effect on the outcome measure with almost a 14% increase in P1s treated with a 20% reduction in the population's RBC demands (Figure 4 A).

Changes in stock level, overall casualty number and proportion of P1s generated a medium effect on the percentage of P1s treated within an hour, with a small or

unappreciable effect occurring with changes to the remaining factors. The predominant effect across all inputs was to produce a greater reduction in this outcome measure when the factor value was increased than occurred in the reverse scenario. Stock level was the only input factor to produce a positive effect on treatment rate when increased. The only exception to this was in instances where the time to assess and gain intravenous access was considered, which showed a positive effect on P1s treated when both increased and decreased from the baseline value, indicating either the factor to be an unstable input or have a less uniform distribution compared with the other input factors.

In terms of P2s treated within four hours of arrival, an overall similar pattern of effects was observed. Notable exceptions were the initial RBC stock level and the proportion of P1s. These factors, along with the percentage of bleeding casualties (as noted with the P1 analysis) inferred the greatest influence, with a large effect on the outcome measures. In comparison, overall demand volume, casualty number and prevalence of the type O blood group in the casualty population were seen to have a medium effect on the outcomes.

The overall percentages of bleeding casualties treated within six and twelve hours were also investigated as additional outcome measures for the study (Figure 4 C & D). This allowed further insight into the system performance and whether given more time, casualty RBC demands could eventually be met if they had not already. The treatment percentages followed the same pattern for each input factor at both time points. As was the case for the treatment of P2s, the rate of bleeding and the initial RBC stock level generated the greatest effect when varied and the prevalence of the type O blood group in the casualty population continued to have a medium effect on treatment percentages. Furthermore, the overall RBC demand volume also produced a large effect on both outcome measures as was the case for P1s treated within the hour.

6. Discussion

6.1. Study Findings

We have developed the first working simulation model of red blood cell provision at a major trauma centre following a mass casualty event. Building and developing the model required a number of iterations to ensure it operated correctly and as originally planned. This involved a stringent process of testing, modification and retesting, followed by repeated inspection of the code and simulation animation prior to verification by a panel of experts experienced with the transfusion process in these events. Having verified and tested the model, we completed the study objective by performing various validation exercises. These included a black-box comparison study and an experimental analysis of the model inputs and outputs, improving both our understanding of this complex system and our confidence in the model.

The comparison study was performed using the largest UK mainland based MCE in over half a century and saw the simulation deliver accurate results when compared to real-life events across all assessable outputs (Aylwin, König et al. 2006). Although P2 casualties could not be directly assessed in this investigation, the additional measures of individual and overall mean time to meet casualty RBC demand examined assured us of the model's performance and its potential as a future planning tool. The need for which was highlighted by the significant consumption of type O universal donor RBCs in the hours following the 7/7 event, an experience replicated by our model. The MTCs response that day included a number of RBC restocks during the hours following the event, without which, type O RBC levels could have risked reaching exhaustion. Contingency planning for such an event is in our opinion vital for future events where restocking may be disrupted or prevented entirely.

The final component of the model building process involved an initial experimentation exercise via a sensitivity analysis. This was in essence, a limited search of the model's solution space, with set variations made across all inputs to determine their overall level of influence within the model. This search revealed the five factors displaying the greatest influence on outcomes, these being: Percentage of bleeding casualties, individual casualty RBC demand volume, proportion of P1s admitted to the MTC, casualties with blood group O and the level of RBC stock available on-shelf at the MTC. Presently, 10 of the 12 model inputs may be influenced by MCE planners, however, the surprisingly relatively small response in terms of outcomes seen when varying the other

potentially modifiable inputs such as staffing levels, time to transfuse and assessment time, indicate system changes in the strategy of the transfusion response, as opposed to physical resources other than blood, offer the greatest potential for system improvement.

The principle relationship evident throughout the experimental results was that more units of blood on shelf equates to better outcomes, be it through less demand on held stocks by the casualties received or a higher general stock hold at the MTC from the start. From the five most influential factors within the model (irrespective of effect size) - the percentage of bleeding casualties and their individual RBC demands are currently beyond our direct control. Proportion of priority 1 to 2 casualties, number of type O casualties received and stock hold however, are accessible to planners as modifiable factors in an MTC's response to an event. This has therefore been the subject of further investigation using the developed model.

To date, experimental work using our model has specifically focused on strategies to manage MTC stock hold. The number of type O casualties received can be considered a component of this experimentation, given the solution to this issue is maintaining greater volumes of type O blood within the overall RBC stock hold (Glasgow, Vasilakis et al. 2015, Glasgow, Vasilakis et al. 2016). Although the holding of greater RBC stocks on-shelf at an MTC is always a possibility in times of increased threat of an MCE occurring, the challenge with increased stock hold comes with the financial implications and to an extent, when considering massive volumes, the logistics of continuously storing RBCs and other blood products on-shelf at an MTC due to their refrigeration requirements and finite on-shelf lifespan. Such barriers would make very high stock holds impractical outside of periods of heightened MCE threat. Similarly, given the importance of type O RBCs as emergency universal donor blood, combined with its dominance in the population - being the most common UK blood group, increasing availability through stockpiling this precious resource would be limited by the same issues (NHSBT 2010).

Our previously published work using this model, has identified that early restocking of RBC supplies following an event using a push over pull approach from central blood stockists to regional MTCs, delivers comparable outcomes to maintaining the equivalent RBC stock levels on-shelf, if performed in a timely manner (Glasgow, Vasilakis et al. 2016). This study-derived approach therefore eliminates the day-to-day burden on MTC transfusion services and the associated costs without impacting on patient care. Direct consultation with policy makers mean this strategy can now be introduced as a part of an automated response in future MCEs (Glasgow, Vasilakis et al. 2016).

Similarly, manipulating the proportion of P1 and P2 casualties received to relieve MTC RBC demand burden is also theoretically modifiable through the implementation of a casualty distribution plan. This could involve an approach whereby P2s are allocated solely to smaller trauma centres, whilst reserving MTCs for only the most severely injured and highest RBC consuming P1 casualties. Such experimentation with this model has not been done as yet, but illustrates the potential for the development of a variety of policies, which together, could potentially absorb a significant amount of the strain placed on transfusion services in even moderately sized MCEs.

Further more radical solutions to managing on shelf stock levels which have been considered through our modelling experimentation include the use of rationing the in-hospital supply of RBCs to individual casualties to preserve stock. This model strategy indicated the overall casualty treatment rates in significantly sized MCEs could be increased above and beyond the baseline level. Furthermore, specifically limiting individual casualty receipt of emergency type O RBCs was found to prolong on-shelf supplies of this key resource (the model's surrogate for time to reach surge capacity) as well as increase overall casualty treatment rates in lesser sized MCEs (Glasgow, Vasilakis et al. 2015). Although such a strategy is not a part of standard practice at present, such a consideration may be required in the future should a situation of such overwhelming demand present that systems were unable to cope without an extreme response.

6.2. Limitations

Any model is a simplification of a real-life process or system to be used as a means of understanding a system better using a more intuitive format. As such, many of the assumptions discussed in the model's development were applied in order to maintain simplicity in the system and meet the overall study objective. There are therefore, a number of limitations which should be appreciated when interpreting the results of this study. Firstly, capacity limits in terms of medical staffing or beds were not incorporated into the model, despite the fact this would likely become a significant issue, especially when considering experimentation with more extreme casualty loads where they would likely impact on RBC delivery times within an MTC.

Secondly, there were system elements which were not included in the model design which could be significant even in more conservatively sized events. These included elements such the provision of components other than RBCs and random failures within the system's operations. Modern resuscitative techniques rely heavily on the provision of other blood components such as plasma and platelets, without which, RBC consumption may be significantly increased due to ongoing blood loss. Whereas, system failures such as blood sampling errors are also not uncommon in these events and with dependence on automated systems there is always the potential for machinery to breakdown or malfunction (Darvall 2003). The latter could have potentially catastrophic effects on system capacity and efficiency, as tasks are required to be performed manually by a limited number of staff. The impact of a change in staff numbers in this instance could be much more significant than observed during the model's sensitivity analysis.

Finally, the black-box comparison validation was limited by the relatively small sample of bleeding casualties experienced by the RLH on the day of the 2005 attacks. This was further confounded, as discussed earlier due to the fact no P2s received at the MTC required a transfusion within the first 72 hours following the event. Furthermore, although every effort was made to gather as much data as possible, the length of time which has passed since the event added to the challenge of acquiring and checking the reliability of all the information collected, all of which could have potentially introduced errors into the validation process.

6.3. Further Research

Future experimental work based on the findings of this study should focus specifically on targeting the 'system levers' and 'supply levels' identified within the model that represent feasible solutions for the real-world system. Specifically, as mentioned, the other key area of influence within the model currently available to planners to manipulate in the aftermath of an MCE is the MTC distribution of P1:P2 casualties. Whilst London is formed of the London trauma network consisting of four MTCs, other regions in the UK operate off single centres (McCullough, Haycock et al. 2014). The model was specifically designed not to be London centric in order for its results to remain applicable across the country and potentially internationally, however, further experimentation could involve the investigation of the impact MTC density may have on performance outcomes regionally when the ratio of P1:P2 casualties received is considered.

Alternatively, experiments may consist of further expanding the model to investigate the effect of incorporating blood products other than RBCs such as plasma and platelets on the system's capacity to cope. Although ongoing discussions with policy makers following publication of the RBC restocking findings may influence such experimentation, the engagement of those involved with translating this research into practice is promising for any future studies.

6.4. Conclusion

Despite the identified limitations, a practical model of a major trauma centre transfusion system has been designed and developed in-line with the study objective through a fully transparent process using industry recommended best-practice guidelines. The model was thoroughly verified, tested and validated for purpose and appears to perform well with respect to its outcome measures. Upon reflection, this study highlighted the valuable opportunities that exist through using systems modelling and simulation as a means of bringing together teams from different disciplines, combining a diverse knowledge base and utilising access to rare empirical data with the aim of improving our understanding of the new challenges we are facing. The

application of this form of operational research to this evolving field has been well received amongst the healthcare community and, given its success in both increasing the understanding of the system as well as designing improved systems for managing these catastrophic events, greater consideration should be given for further studies of mass casualty event response. The aim should be to further explore and expand the model and utilise this methodology to improve our response following these challenging events, which although rare, are of increasing prevalence.

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